BMJ Global Health

COVID-19 vaccine trials with children: ethics pointers

Caesar Alimisnya Atuire ,[1] Sofía P Salas,[2] Katharine Wright,[3] J Radeino Ambe ,[4] Jantina de Vries[5]

To cite: Atuire CA, Salas SP, Wright K, *et al*. COVID-19 vaccine trials with children: ethics pointers. *BMJ Global Health* 2022;**7**:e007466. doi:10.1136/bmjgh-2021-007466

Handling editor Seye Abimbola

Received 20 September 2021
Accepted 16 December 2021

[1]Department of Philosophy and Classics, University of Ghana, Accra, Ghana
[2]Center of Bioethics, Faculty of Medicine, Clínica Alemana, Universidad del Desarrollo, Santiago de Chile, Chile
[3]Nuffield Council on Bioethics, London, UK
[4]Department of Public Health, Capella University, Minneapolis, Minnesota, USA
[5]Department of Medicine, University of Cape Town, Cape Town, South Africa

Correspondence to
Dr Caesar Alimisnya Atuire; atuire.ca@gmail.com

ABSTRACT

As healthcare authorities around the world strive to get as many citizens as possible vaccinated against the SAR-CoV-2 virus, many countries have begun including children in the population groups to be vaccinated. Properly designed clinical trials involving children are important to ensure safety, efficacy, and dosage of therapies in (developing) children. Within the complex health, social, and political scenario of the ongoing pandemic, ethics committees and policy makers in low-income and middle-income settings need to consider additional ethical questions when called on to review phase III COVID-19 vaccine trials involving in children. We set out some of the ethical questions to keep in mind before, during, and after the implementation of phase III COVID-19 vaccine trials in limited resource settings. Specifically, we discuss and offer succinct answers to the following questions: How relevant will the trial vaccine be for the population participating in the trial? Should vaccines that have not been approved for use among adults be approved for use in trials with children? Which children should be involved in COVID-19 vaccine trials? What criteria of informed consent are to be adopted with minors? Placebo versus an existing already approved vaccine? What specific duties of ancillary care should be taken into consideration for COVID-19 vaccines especially in low-income and middle-income countries? The answers we offer are considerations that can serve as 'things to think about' when reviewing or implementing COVID-19 trials involving children in low-income settings.

Summary box

- Safe and effective COVID-19 vaccines for children are needed, both to offer direct benefit to children, and for wider public health benefit.
- Many ethics committees in low-income and middle-income countries do not feel well-placed to review clinical trial proposals for such vaccines, especially in the politically charged context of a pandemic.
- This article shares insights and key recommendations from members of the COVID-19 Clinical Research Coalition ethics working group, identifying elements of vaccine trial proposals that ethics committees should particularly scrutinise.
- These include: likely future cost and availability of the trial vaccine in the relevant country; the need to involve children from diverse backgrounds; culturally sensitive consent processes; when placebo may, or may not, be acceptable; and the need for community engagement to ensure sensitive plans for meeting ancillary care needs.
- The value of close liaison with regulatory bodies is also highlighted, in order to ensure ethics committees have access to relevant technical advice

BACKGROUND

As the number of persons vaccinated against COVID-19 around the world increases and the number of approved vaccines for use among adults rises, there is growing recognition of the need to extend vaccination campaigns to children. Emergency use authorisation has already been provided by various national regulators to allow for the use of the Pfizer-BioNTech and Moderna vaccines in children 12 years of age and older. Furthermore, vaccine trials involving younger children and testing different vaccines are underway in various countries.[1] While most of these trials are currently conducted in high-income countries, it is likely—and necessary—that COVID-19 vaccine trials involving children will increasingly be extended to lower/middle-income countries (LMICs) in order to ensure that vaccines are effective in these different populations and contexts. In that case, ethics committees and policy makers will be faced with the review of trial proposals that not only raise potentially challenging ethical questions (as in all interventional studies with children),[2] but where those questions are further complicated by a number of factors associated with the pandemic context in a low-resource setting. These include the urgency to act (which may add to the pressure experienced by those tasked with reviewing studies); a lack of clarity as to where future benefit from the studies may accrue (given current concerns about inequality of vaccine access); and, more broadly, the impact of inequalities in terms of scientific capacity and economic power which may skew the ability of some committees to provide independent reviews.

As members of the ethics working group of the COVID-19 Clinical Research Coalition (which brings together expertise in

research ethics from across a wide range of LMICs), we are aware that ethics committees in LMICs do not all feel well-placed to review such trial proposals. Our goal in this paper is to share our insights and key recommendations for the elements of vaccine trial proposals that ethics committees should particularly scrutinise when reviewing such proposals. Below we set out some ethical questions and possible replies that researchers and ethics review committees might need to keep in mind before, during and after the implementation of phase III vaccine clinical trials with children. We use the term 'children' in this article to refer to persons who cannot legally give consent because of their age: this will commonly be those under the age of 18, although depending on jurisdiction this may vary from 16 to 21. Our concern is especially with children living in lower-income and middle-income settings.

It is *not* our goal to discuss the wider ethical debate about *when*, amidst global scarcity of vaccines, countries should start vaccinating persons under 16 or 18 years.[3] The question we address is a different one. Vaccination campaigns among children require the availability of vaccines that have been tested and approved as safe and effective for use among children. It is well recognised that children's immune systems are not just smaller versions of adult ones.[4] Younger children are developmentally, physiologically, and psychologically different from adults, and their immune system and physiology changes during different developmental stages, as they approach adulthood. Clinical trials generate knowledge about which health interventions are safe and effective for children at different developmental stages, thus protecting their health and well-being. Nevertheless, these trials raise ethical questions that are different to trials among adults.

Historically, people have been cautious about including children in clinical trials. Children have long been regarded as inherently vulnerable in research, both because of their reliance on others to meet their basic needs, and because their ability to make their own decisions is still developing.[5] These concerns about the risks of involving children in research have resulted in restrictive approaches designed to protect children that, in practice, may lead to the conclusion that it is 'safer' not to undertake research with children at all. However, the result of not including children in properly designed research is that they end up being treated without an adequate evidence base as to the safety, efficacy and dosage of therapies in (developing) children—thus potentially making children *more* vulnerable through exposure to unsafe care. In recognition of this dilemma, there has been considerable debate in recent years over how to ensure that such research can be conducted ethically. Key developments include an emphasis on working *with* children and families to design studies in ways that are appropriately child-friendly, and to ensure that children are involved, in ways suitable for their age and state of emotional and psychological development, in decisions about their own participation.[6]

The CIOMS Ethical Guidelines (2016, Guideline 17) recommend that 'children and adolescents must be included in health-related research unless a good scientific reason justifies their exclusion',[7] while emphasising the importance of minimising risks and, where relevant, waiting first for data from adult trials. A more restrictive position is presented, for instance, by the national South African Health Research Ethics guidelines, which propose that research should involve children only if the research cannot equally be conducted with adults, if the outcome of the research is directly relevant for children, and if the risk is reasonable—and preferably, minimal.[8] Importantly, these and other guidelines suggest that since children in general are less able than adults to protect their own interests, additional safeguards are needed to ensure they are not exploited.

REASONS FOR CARRYING OUT COVID-19 VACCINE TRIALS WITH CHILDREN

There are several reasons why COVID-19 vaccine trials should involve children. These all relate to a consideration of whether and how being vaccinated could directly or indirectly be of benefit to children's health. If proven effective, vaccines would clearly offer direct benefits to children who for various reasons have an increased risk of severe illness or death from COVID-19. There is currently limited information on children since fewer children have been affected with severe illness; however, there is increasingly clear evidence that children living with pre-existing health conditions, including complex disability with high healthcare needs,[9] are at higher risk from developing COVID-19 complications. The evidence regarding the risks of 'long-COVID' on children is still developing but highlights a further non-negligible source of concern.[10] Furthermore, with the emergence of new variants, and with increasing concerns about the effect of long-COVID on children, it is possible that effective vaccines would confer direct physical health benefits to all children and not just those at increased risk of severe disease. Vaccines can also reduce the impact of COVID-19 infection in children, by putting them in a safer condition to socialise normally both with their peers and older persons, and in particular by reducing the risk of extended absences from school. The ability to socialise is important for the mental health, growth, development, and overall well-being of children. Thus, a safe and effective vaccine for children is of direct benefit to them.

Additionally, vaccinated children can also protect those that cannot be vaccinated due to medical conditions, thus also protecting others who live with them or attend school with them. Furthermore, beyond direct potential benefit to children, there is also a strong public health reason to ensure that safe and effective vaccines are available for children. Namely, even though the earlier goal of herd immunity now seems like a mirage and the SARS-CoV-2 virus and its variants are more likely to become endemic,[11] a failure to vaccinate children—which would allow the virus to spread freely in a large part of the population—could increase the possibility that new variants emerge that could either be more contagious or resistant to existing vaccines and therapeutics. This point is particularly relevant in many African countries where

up to 40% of the population is younger than 16 years of age. Thus, there are also important public benefits to ensuring that vaccines are developed that are safe and effective for use in children.

In the remainder of this paper, we discuss the most important considerations for ethics committees reviewing proposals that involve children in COVID-19 vaccine clinical trials.

SOME ETHICS Q&A WHEN IMPLEMENTING COVID-19 VACCINE TRIALS WITH CHILDREN

Guidelines and normative documents on vaccine clinical trials with children in many countries and regions were written before the COVID-19 outbreak.[12–14] The scale of the threat posed by the SARS-CoV-2 virus, however, cutting across borders, age groups, race, socioeconomic situation, gender and sexual orientation, is unprecedented. There is an urgent need to immunise as many people as possible and as quickly as possible. Yet, there is an equally important need to avoid exposing people to excessive risks, especially children.[15] Moreover in some countries, as some vaccines are undergoing clinical trials involving children, other vaccines have already been approved for use among adults and some minors. In other countries, mostly LMICs, vaccines are yet to be made available even for vulnerable and adult populations.[16] These differences and the impellent need to vaccinate populations generate novel ethical questions that were not at the fore prior to the emergence of the COVID-19 pandemic. Some jurisdictions, for example, the US Food and Drug Administration, offer updated guidelines on COVID-19 clinical trials involving children.[17] Many are yet to do so; thus, it is in this vein that as members of the Ethics Working Group of the COVID-19 Research Coalition we offer some ethical 'things to think about' as researchers and IRBs embark on or follow through with COVID-19 clinical trials involving children.

How relevant will the trial vaccine be for the population participating in the trial?

In a pandemic where no country is immune to COVID-19, the principle of solidarity would suggest that all those who can, should contribute to generating and sharing knowledge that will contribute to saving lives and reducing illness. Yet, an equally important question is whether it is likely that, if approved, the trial vaccine will be available in the country where the vaccine is being tested, or whether (if there is good reason why not) participants and the wider community will have timely access to another, equally effective, vaccine. This question of future access (and the associated question of why *this* study is being conducted in *this* particular country) is a particularly important aspect of the general ethical requirement that research confers 'fair benefits': while in other circumstances it might plausibly be argued that other kinds of benefit might be as valued such as future access to a particular intervention, it is hard to make such a case in the current situation of highly inequitable access to COVID-19 vaccines and therapeutics in many LMICs. Thus, the issue of future cost and likely future availability of the trial vaccine—should it be proven safe and effective—needs to be factored into the ethical deliberations.

Should vaccines that have not been approved for use among adults be approved for use in trials with children?

In order to minimise the risks to which children are exposed, normal practice is to commence trials with children only when a vaccine has already been shown to be safe and effective in adults. This would suggest that only those vaccines that have been approved for use in adults should be used in trials involving children. However, this requirement could constitute a long delay which could hinder global efforts to curb the pandemic—and might thus delay important benefits for children. Moreover, there are vaccines that are intended to be used only in the paediatric population.

The case of novel candidate vaccines that have not yet received approval for use among adults, or for which trials among adults are still ongoing, requires a different ethical evaluation. The challenge here is to weigh the risks posed to child participants in starting trials before more certain data are available from adult trials (thus, eg, potentially including children in trials of ultimately unsuccessful vaccine candidates), and the risks of delaying too long (thereby exposing more children to the direct and indirect harms of COVID-19 discussed earlier in this article). In order to achieve this difficult balancing of risk and prospect of benefit, ethics committees may need to liaise with regulatory authorities, in order to access the appropriate technical expertise. Some experts advise, as part of this fine balancing of risk, that trials should commence with older children first as they are most similar to adults[15]—again this will be a judgement about relative risks of early action versus delay, based on evolving knowledge of the risks of COVID-19 to younger children.

Which children should be involved in COVID-19 vaccine trials?

The SAR-CoV-2 virus can infect all children irrespective of age, health, social conditions, and ethnic background. Even though the outcomes of an infection may differ among children, vaccines are designed to be administered to all children. For reasons of fairness and justice, it is important that vaccines will be proven safe and effective for all children. Therefore, trial participation needs to mirror the demographic, social, ethnic, and health conditions of the geographical areas in which the vaccine would be used if approved, in order to support fair access. This also means that children living with high-risk health conditions and disabilities (whether neurological, genetic, physical, developmental or emotional) equally need to be included. If trials include only healthy children, and yet children living with high-risk conditions will be prioritised during vaccination, there would be a risk of missing evidence about how such children's immune systems respond to the vaccine. The timing of

this will again depend on the weighing of the relative risks of participation/non-participation for children with particular conditions or disabilities: while the default position might be to wait until the vaccine candidate has been proven safe and effective in healthy children, this might not always be appropriate if particular conditions/disabilities put children at exceptionally high risk of harm from COVID-19. Therefore, when reviewing paediatric vaccine trials proposals, reviewers will need to look carefully at which children are included; whether the children most likely to benefit from safe and effective vaccines should also be involved in the research; and if so at what point.

What criteria of informed consent are to be adopted with minors?

Most jurisdictions rely on a parent or guardian to provide informed consent for children to take part in research, with some also allowing for adolescents (eg, 'mature minors' already living independently, or those who meet a threshold of competence) to consent for themselves even though they have not reached the age of majority. In some jurisdictions, both parents' consent may legally be required before a child may take part in research. Ethically, children who are competent to do so should also be part of the consent process, even if in law their parent's consent is sufficient. Younger children should be involved in the decision in a way suitable to their age and understanding, with requirements of how their 'assent' is sought or documented varying from country to country. Such involvement of younger children in the decision-making process should also include respect for a child's wish not to take part.

There may be cases where legal requirements obstruct the enrolment of particular populations or subgroups, for example, where consent must be provided by both parents but it is common for one or both parents to work a long way away from home. In those cases, if there is no scope for seeking a legal waiver, then additional scrutiny must be given to ensuring that a suitably diverse group of children are recruited, despite these barriers to participation.

Ethics committees will need to scrutinise carefully the proposed consent and assent procedures—especially in an environment of politicised resistance against vaccination or widespread lack of vaccine confidence—so that trial enrolment does not put a child in conflict with one or both of their parents (even if, as noted above, the law would permit a child's inclusion on the basis of their own consent alone). Furthermore, when designing appropriate consent models, it is important to consider the context, especially when using standard protocols in different countries. For instance, if girls will be asked to take a pregnancy test as part of the trial protocol, this must be communicated appropriately to both the child and her parents before consent/assent is sought, and implications for confidentiality (eg, whether the result will be shared with parents) made explicit.

Placebo versus an existing already approved vaccine

The nature of the COVID-19 pandemic, the rapid approval and use of different vaccines, and the unequal distribution of vaccines across and within countries, have generated complex ethical questions concerning study designs for vaccine trials. Whereas some ethicists are of the opinion that the use of placebo is 'ethically appropriate' and that researchers are 'not ethically obligated to unblind treatment assignments', this opinion has come under severe criticism from other ethicists.[18]

An important criterion for ethics committees when reviewing such trials is to aim for the best standard of care that is genuinely available for the population. Thus, it might be acceptable for an initial vaccine trial to have a placebo-controlled arm, if there was no other vaccine candidate approved for this specific age. However, when at a country level an emergency approval is granted, it becomes much harder to justify continuing with a placebo-controlled trial, particularly in the midst of the pandemic. In this situation, the ideal trial would be to compare the already approved vaccine with the new vaccine candidate, in the traditional double-arm controlled trial, where this is possible (We say 'where this is possible' because some manufacturers of approved COVID-19 are reticent about the use of their vaccines for trials for new vaccines. This was denounced in an open letter by CEPI in September 2021, published in Nature (https://www.nature.com/articles/d41586-021-02398-6)).[19]

As soon as a new vaccine is granted emergency approval in the country or region where the trial is being deployed, ethics committees should scrutinise proposed plans for unblinding the trial with a view to ensuring that participants in a placebo arm (if applicable) are not disadvantaged.

What specific duties of ancillary care should be taken into consideration for COVID-19 vaccines especially in LMICs?

Vaccine trials generally involve large numbers of participants. In LMICs, children from marginalised and economically poorer communities must be included in trials to ensure that results are as relevant as possible to diverse parts of the population. This generates specific duties of ancillary care that will have to be factored into the ethical evaluations of the trials.[20] The type of ancillary care will differ according to countries. For example, children from lower-income groups may be more likely to present with conditions such as malaria, acute diarrhoea, acute respiratory tract infections, and other conditions related to poverty, and researchers have at least a partial obligation to consider those conditions. Furthermore, children from low-income communities may not have eaten on the day of research—and perhaps their siblings have not either. This is a considerable challenge especially when the COVID-19 pandemic has increased poverty among the most vulnerable. It would be important to assist such children without necessarily turning participation in the trial into an incentive to obtain other forms of assistance. What is important is that researchers

need to carefully consider ancillary care obligations, and ethics committees need to assess whether the ancillary care offered during the trial is reasonable.[21] Forms of stakeholder and community engagement can provide valuable ways of helping identify the appropriate form and scope of any such interventions.

FINAL REMARKS

The COVID-19 pandemic is daily pushing science and ethics into unexplored terrain. In the case of ethics committees, there is the need to draw on existing normative guidelines and to adapt them to the rapid evolution of the pandemic and response measures. As vaccines appear to be successful in reducing deaths and severe illness among adults, a major concern now is how to protect children from getting infected and transmitting the virus, and from falling ill themselves. An important tool is the vaccination of children. Yet, this choice needs to be backed by science and ethics. This brief paper is an effort by a group of ethicists working within the COVID-19 Research Coalition to share concerns and ideas with ethicists who are currently or will soon be reviewing protocols for vaccine trials among children.

Twitter Caesar Alimisnya Atuire @atuire and J Radeino Ambe @J.Radeino Ambe @jennyferambe

Contributors The authors are members of the COVID-19 Research Coalition Ethics WG. The idea to write the paper arose after a presentation by SPS on COVID-19 trials in Chile. CAA worked on the conceptualisation and the initial draft. The draft went through several iterations with SPS, KW, JRA and JdV making important contributions, edits and suggestions. CAA is guarantor of content of this paper.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study does not involve human participants.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article.

ORCID iDs
Caesar Alimisnya Atuire http://orcid.org/0000-0001-6825-6916
J Radeino Ambe http://orcid.org/0000-0002-5780-4662

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